REMARKS

A. Status of the Claims

Claim 1 has been amended and new claims 17-23 have been added; thus, claims 1-5, 10-13 and 16-23 will be pending in the application upon entry of the present amendment. Support for the amendment to claim 1 can be found at least on page 6, lines 17-19 and page 9, lines 24-25. Support for new claims 17 and 18 can be found, at least, on page 7, lines 1-10 and page 8, lines 9-16 of the specification. Support for new claim 19, can be found at least on page 8, line 18 of the specification. Support for new claims 20 and 21 can be found, at least, on page 10, lines 1-10 of the specification. Support for new claims 22 and 23 can be found, at least, on page 10, lines 16-24 of the specification. No new matter has been added.

B. The rejection of claims 1-5, 10-13 and 16 as obvious under 35 U.S.C. § 103(a) over Advani (1997) in view of Carroll should be withdrawn

Applicants acknowledge that the sole outstanding rejection of the claims is the rejection of claims 1-5, 10-13 and 16 under 35 U.S.C. § 103(a) over Advani, Int. J. Oncol. Rad. Biol. Phys. (1997) (hereinafter, the "Advani abstract") in view of Carroll, et al., Ann. Surg. 224:323-330 (1996) (hereinafter, "Carroll").

Asserted rejection

The Examiner maintained the rejection of all pending claims under 35 U.S.C. § 103(a) over the Advani abstract in view of Carroll. In supporting remarks, the Examiner acknowledged that Advani (1997) "does not explicitly teach that the attenuated HSV virus [R7020] could be used to treat a non-CNS tumor in vivo." Office Action at page 3. Further, the Examiner acknowledged that Advani does not teach "the particular amount of the HSV which would be a therapeutically effective amount for reducing tumor mass." *Id.* The Examiner continues to assert that "Carroll teaches treatment of non-CNS tumor using an attenuated HSV (hrR3). Specifically, Carroll teaches a method for *infecting* colon carcinoma liver metastasis by administering an attenuated HSV directly to the tumor (e.g., see abstract)." *Id.* at 4. The Examiner concludes that "[o]ne of ordinary skill in the art would have been motivated to modify the method of Advani to treat a non-CNS cancer because Carroll teaches that attenuated HSVs can be used to treat non-CNS-type tumors." Office Action at page 3-4. Applicants continue to disagree with the Examiner's position.

The rejection fails to address all claim elements

Applicants respectfully submit that the Examiner has failed to establish a *prima facie* basis for the asserted obviousness of the claimed subject matter. In order to establish a *prima facie* basis for obviousness, the Examiner must identify how the prior art reference(s) teach or suggest all the claim limitations (*see, e.g.,* MPEP §2143.03). To formulate a proper rejection "[a]ll words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). In the instant case, the Examiner has not established (1) that either the Advani abstract or Carroll expressly or inherently disclose, or suggest, the reduction of any tumor mass; or (2) that either the Advani abstract or Carroll disclose or suggest that administration to a patient of any HSV modified in accordance with the claims would be safe. Because each of the enumerated points is a limitation of the rejected claims, the rejection fails to address all claim limitations and, thus, no *prima facie* case for obviousness has been set forth on the record.

Cited art does not disclose or suggest tumor mass reduction

With respect to the first enumerated point, Applicants maintain that the Advani abstract does not disclose or suggest that HSV R7020, the sole HSV disclosed in that reference that conforms to the HSV of the pending claims, reduces the mass of any tumor. Beyond failing to disclose or suggest the use of any HSV to treat a non-CNS tumor, the Advani abstract fails to disclose or suggest the use of any HSV to reduce a glioma tumor mass. In the attached declaration under 37 C.F.R. § 1.132, Dr. Roizman notes that the Advani abstract is completely silent on the issue of tumor mass reduction. Roizman declaration, paragraph 7. Therefore, the Advani abstract does not expressly disclose that HSV R7020 reduces any tumor mass.

Applicants submit that the Advani abstract also fails to inherently disclose that HSV R7020, or any HSV defined by the pending claims, reduces any tumor mass. "'In relying upon the theory of inherency, the Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art.'" M.P.E.P. § 2112 (IV), quoting Ex parte Levy, 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Interf. 1990) (emphasis in original). In the present case, the Advani abstract discloses data relating to HSV R7020 for up to 7 days post-infection. In contrast, the specification discloses that it took 13 days after infection to begin to see SQ 20b tumor mass reduction (*see* Roizman declaration at

paragraphs 6 and 7). Thus, the Examiner has not provided evidence establishing that the experimental results disclosed in the Advani abstract inherently disclose the reduction of a tumor mass attributable to HSV R7020.

The Examiner relied on the following statement in the Advani abstract as a basis for concluding that the abstract disclosed a method of using HSV R7020 to reduce a tumor mass. "Herein we demonstrate radiation enhanced viral replication as one of the interactive effects of combining IR and attenuated HSV in treating glioma xenografts and a potential therapeutic motif in the treatment of gliomas." Office Action at page 3. The recitation of a "treatment" does not establish that a tumor mass reduction necessarily flowed from Advani's disclosure of the administration of HSV R7020 to a xenograft-bearing mouse. The Roizman declaration, at paragraph 7, establishes that tumor treatments could result in (1) reduction of tumor growth rate; or (2) tumor stasis limited to simply halting tumor growth. Attached to the Roizman declaration as Exhibit D is U.S. Patent No. 5,342,947, which Dr. Roizman cites (paragraph 8) as evidence that tumor stasis treatment was known to halt tumor growth, but not involve tumor mass reduction.

In addition, those of ordinary skill in the art would understand that tumor treatments resulting in a reduction in tumor mass must provide sufficient virus to generate a rate of tumor cell death that exceeded the rate of tumor cell growth without causing death or disease in the subject. As noted in the Roizman declaration at paragraph 12, one of ordinary skill in the art could not have concluded that the single disclosed dose of 2×10^7 pfu HSV R7020 would necessarily lead to tumor mass reduction when the Advani abstract did not even precisely define that tumor mass, the quantity of tumor cells found in the tumor, or the cytotoxicity of HSV R7020 *in vivo* (only HSV replication levels were determined). Rather, the Advani abstract disclosed that tumors were ">200 mm^3," or greater than 200 mm^3. Without knowing how many tumor cells were growing, one of skill could not have concluded that 2×10^7 pfu HSV R7020 would result in a rate of tumor cell death that exceeded the rate of tumor cell growth, thereby leading to tumor mass reduction. The Examiner recognized this fact in remarks found at pages 17-18 of the Office Action mailed October 11, 2002 in this matter: "Advani (1997 and 1998) does not disclose that the rate of killing is faster than the rate of growth, which is required to result in the reduction of tumor mass." Nonetheless, in the outstanding final Office Action at page 5 ,the Examiner stated that "although Advani does not explicitly teach a reduction of tumor mass, performing the method taught by Advani to

treat non-CNS tumors (taught by Carroll) *wherein the method is optimized for greatest efficacy* . . . would necessarily result in tumor mass reduction." Emphasis added. On its face, the Examiner's statement is insufficient to establish that the Advani abstract inherently disclosed tumor mass reduction. In order for tumor mass reduction to be inherent even the unoptimized method must lead to reduction because reduction must nessiaryly flow from the method. Even if *optimization* of the methods of Advani did necessarily result in tumor mass reduction, moreover, Advani still does not inherently disclose a method for tumor mass reduction. See M.P.E.P. § 2112 (IV), which states that:

> "The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (*reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art*) . . . ." Emphasis added.

Moreover, the skilled artisan would recognize that tumor mass reduction does not necessarily result from the method of Advani (or Carroll), even when "optimized," and Applicants have provided evidence of this fact (*see, e.g.*, the enclosed Roizman declaration at paragraph 13). Even if *optimization* of the methods of Advani did necessarily result in tumor mass reduction, moreover, Advani still does not inherently disclose a method for tumor mass reduction. For all of the foregoing reasons, the Advani abstract did not disclose, expressly or inherently, the use of HSV R7020 in a tumor treatment method that led to a reduction in tumor mass.

Cited art does not disclose or suggest HSV is safe for administration

The Advani abstract does not disclose, expressly or inherently, a safe dose of an HSV, as recited in the pending claims. A safe dose, as would be understood by one of ordinary skill in the art, is a dose that does not cause death or disease in the subject. The preceding discussion established that the Advani abstract did not provide evidence that HSV R7020 was efficacious in reducing a glioma tumor mass. The Advani abstract also failed to disclose, expressly or inherently, that the administered dose of 2×10^7 pfu HSV R7020 would be safe insofar as it would not exhibit unacceptable toxicity towards healthy cells of the treated subject. The Advani abstract confined its disclosure to an examination of tumor tissue. The Advani abstract provides no disclosure of any effect, or absence of an effect, of HSV R7020 on any non-tumor tissue or on the health of any injected mice. Accordingly, one of ordinary

skill in the art would not have the view that the Advani abstract disclosure of the administration of 2×10^7 pfu HSV R7020 is safe.

The Advani abstract and Carroll are not properly combinable

The disclosures of the Advani abstract and Carroll cannot properly be combined on the basis that each reference discloses an attenuated HSV because the mechanisms of attenuation for these HSVs are scientifically unrelated. In rejecting the claims as obvious under 35 U.S.C. § 103(a), the Examiner relied on the Advani abstract in combination with Carroll. Carroll, however, does not remedy the defects in the Advani abstract, such as the failure to disclose or suggest that an HSV according to the pending claims would be useful in reducing a tumor mass or that such an HSV would be sufficiently safe to yield a dose that would be a therapeutically effective amount. The Examiner relied on Carroll as disclosing the use of an attenuated HSV (*i.e.*, HSV hrR3) to treat a non-CNS tumor. Beyond failing to remedy either defect in the Advani abstract noted above, Carroll cannot be properly combined with the Advani abstract in support of the rejection.

The Advani abstract discloses HSV R7020, an HSV in accordance with the claims. The sole virus disclosed in Carroll, HSV hrR3, is not an HSV in accordance with the claims, and the Examiner has not asserted otherwise. The Examiner has effectively asserted that any attenuated HSV can be substituted for any other attenuated HSV, and Applicants disagree with that position. As noted in the Roizman declaration at paragraphs 20-26, the mechanisms of attenuation of Advani's HSV R7020 and Carroll's HSV hrR3 are completely different. Advani's HSV R7020 is a multi-mutated virus that has a deletion of an inverted repeat and the genes, including a $\gamma_1 34.5$ gene, located therein. Roizman declaration, paragraph 21. In contrast, HSV hrR3 has a mutation in the $U_L 39$ gene leading to loss of viral ribonucleotide reductase. Roizman declaration, paragraph 23. As explained by Dr. Roizman in paragraphs 23-26 of the declaration, the mechanisms of attenuation for HSV R7020 (Advani) and HSV hrR3 (Carroll) are distinct. The Roizman declaration states that, for these reasons, one of ordinary skill in the art would not look to Carroll as a guide for modifying any method disclosed in the Advani abstract. Accordingly, there is no proper reason for combining the disclosures of the Advani abstract and Carroll.

Carroll teaches away from the claim methods

Applicants further submit that Carroll teaches away from the claimed methods. A skilled artisan, having reviewed the disclosure of Carroll, would have questioned the safety associated with attenuated HSV such as hrR3 (paragraph 29 of the enclosed Roizman declaration). *In vivo* studies reported in Carroll indicated that HSV hrR3 infected normal tissue in addition to tumor tissue. Thus, Carroll teaches that an attenuated HSV (HSV hrR3) administered *in vivo* is not effective in infecting non-CNS tumor cells while being safe in not infecting healthy cells. As further evidence of this conclusion an addendum to the paper containing a discussion of the paper by researchers in the field, and the authors of Carroll themselves, calls into question whether the methods disclosed in Carroll would be safe (see paragraph 29 of the enclosed Roizman declaration and pages 5-7 of Carroll). Thus, even if a *prima facie* basis for the obviousness rejection were set forth on the record, the disclosure of the Advani abstract in view of Carroll still fails to render obvious the claimed methods.

For all of the foregoing reasons, Applicants submit that the rejection of each of claims 1-5, 10-13 and 16 as obvious under 35 U.S.C. § 103(a) over the Advani abstract in view of Carroll has been overcome and the rejection should be withdrawn.

C. Conclusion

For all of the foregoing reasons, Applicants submit that all outstanding rejections and objections have been overcome and claims 1-5, 10-13, and 16-23 are in condition for allowance. An early notice thereof is respectfully solicited. Should any fees be deemed necessary, the Commissioner is authorized to charge any such fees to our Deposit Account No. 13-2855, under order no. 27373/36638A. If the Examiner has any questions or concerns, he is invited to contact William Merkel or the undersigned at the telephone number below.

Dated: February 17, 2009

Respectfully submitted,

By 

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